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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/056,348	BURCH ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38 and 47-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38 and 47-65* is/are rejected.

7)☒ Claim(s) *57 and 58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/19/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 1-37 and 39-46 have been cancelled.

Claims 53-65 have been added as filed on 2/26/08.

Claims 38, and 47-65 are currently pending.

Claims 38, and 47-65 are being examined in this application.

Election/Restrictions

2. Upon further consideration, the previously set forth Requirement for Species Election (mailed 6/4/08) is withdrawn. Thus, applicant's election of species (Reply entered 7/7/08) is moot.

Priority

3. This application is a continuation of 09/154,354 (filed 9/17/1998; now US Patent 6,552,031), which claims benefit of 60/059,195 (filed 9/17/1997).

Information Disclosure Statement

4. The IDS filed on 11/19/07 has been considered. See the attached PTO 1449 form.

Claim Objection(s) / Rejection(s) Withdrawn

5. In light of applicants' amendments to the claims and supporting arguments, the following claim rejection as set forth in the previous office action is withdrawn:

A.) Claims 38 and 47-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

B.) Claims 38 and 47-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

C.) Claims 38, 47-50 and 52 are rejected under **35 U.S.C. 102(b)** as being anticipated by Mayer et al (US 5,840,731; 11/24/1998; filed on 8/2/1995). However, a new rejection (as necessitated by applicant's amendment to the claims) over the Mayer reference under 35 USC 103(a) is set forth below.

Claim Rejections Maintained

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Baker, Friedel and Eversmeyer

8. Claims **38**, **47**, **48**, **50-52, 62** and **63** as amended or originally filed are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baker** et al., (US Patent 4,569,937; 2/11/1986; cited previously), in view of **Friedel** et al (Drugs. 1993. Vol. 45 (1): 131-156; cited previously) and **Eversmeyer** et al., (American Journal of Medicine. Aug. 1993, Vol. 95: 10S-18S; cited previously). The previous rejection over claims 38, 47, 48 and 50-52 is maintained for the reasons of record advanced in the previous office actions as well as for the reasons below. The rejection over claims 62 and 63 is necessitated by applicant's amendment to the claims.

Baker et al. teach pharmaceutical compositions for relieving pain in humans or mammals (e.g. mice, rats etc.) comprising a combination of:

a.) a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; mice data in col. 8-10; patent claims), or a pharmaceutically acceptable salt thereof (reads on the salt of **clm 48**); and

b.) ibuprofen (a non-steroidal anti-inflammatory drug or NSAID: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof,

in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present **claims 47** and **63**: See col. 2) with oxycodone amounts of about 5 mgs-600mgs (compare to present **claims 46** and **52**).

The Baker reference also teaches various dosage formulations such as the ones listed on column 4 (e.g. Examples 1-4), which tablet formulation "consists" of an oxycodone salt, Ibuprofen, and "at least one pharmaceutically acceptable excipient" including "microcrystalline cellulose", "starch", and "stearic acid". These formulations read on the oral dosage form of the instant **claim 38** except Ibuprofen is included instead of nabumetone. As recited in the various

Examples (col.4), the amount of Ibuprofen (a NSAID compound) ranges from 60-300 mg, which range reads on the range recited in **claim 51**.

The dosage formulation of Baker also inherently teaches inclusion of oxycodone and at least one salt thereof as recited in **claim 62**, because it is an inherent property of the oxycodone salt (such as Oxycodone HCl) to comprise the Oxycodone compound itself. Thus, the formulation of the Baker reference comprises Oxycodone and at least a salt thereof.

The Baker reference further teaches oral administration (reads on the instant oral dosage form of **claim 38**), which can be co-administered in a single dosage form (e.g. see col. 3-8) or sequentially administered (e.g. see i.e. col. 8-9; mice are dosed sequentially...). The oral dosage forms include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4), which reads on the sustained release formulations of **claim 50**. The Baker et al. reference also teaches that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is unexpectedly enhanced or synergistic i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components, thereby permitting reduced dosages of narcotic analgesics (e.g. oxycodone) AND which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components resulting from high dosages of oxycodone or NSAID's such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32). Accordingly, Baker would teach the use of therapeutic and sub-therapeutic amounts of oxycodone and/or ibuprofen in view of the synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular

patient., including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

The Baker reference does not explicitly teach an oral analgesic composition comprising nabumetone instead of ibuprofen. The Baker reference also does not explicitly teach an oral dosage formulation comprising of nabumetone and at least one salt thereof as recited in the instant claims.

However, **Friedel** et al. teach that nabumetone (and/or pharmaceutical acceptable salt thereof) possesses the typical pharmacodynamic properties of the nonsteroidal class of anti-inflammatory (NSAID) drugs including intrinsic analgesic and antipyretic activity being demonstrated in animal studies and in humans with the following advantages over other NSAIDS:

a. does not exert a significant direct toxic effect on the gastric mucosa during absorption;

b. in studies, produced a lower incidence of gastrointestinal erosions or microbleeding than aspirin, naproxen, piroxicam and ibuprofen; and

c. more recently clinical data further confirmed the efficacy and tolerability of nabumetone ; "Thus, the drug (e.g. nabumetone and/or pharmaceutical acceptable salt thereof) should now be considered a well established member of this group of agents (e.g. NSAIDS) for the treatment of painful rheumatic and inflammatory conditions". See e.g. Abstract, pages 132-133 as well as the remainder of Friedel.

In addition, the Friedel reference also teaches various dosage amounts (such as 1000 mg-1500 mg) of nabumetone can be used for various treatment depending on the severity of the symptoms (e.g. p.133, bottom), which reads on the amount of nabumetone as recited in **claim 51**.

Similarly, **Eversmeyer** et al. teach that nabumetone is equally efficacious in the treatment of arthritic pain patients (e.g. osteo/rheumatoid arthritis) but has shown to be more safe, with reduced side-effects (e.g. dyspepsia, ulcers, reduced hemoglobin, gastritis etc.). See Eversmeyer et al. Abstract and disclosed studies.

Accordingly, one of ordinary skill in the art would have been motivated to substitute nabumetone and/or pharmaceutical acceptable salt thereof (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Friedel and/or Eversmeyer reference teachings that nabumetone is equally efficacious, but is safer with less side effects (e.g. as compared to ibuprofen).

Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting the NSAID nabumetone (and/or pharmaceutical acceptable salt thereof) for the NSAID ibuprofen in light of the benefits of nabumetone (increased safety/decreased side effect as compared to ibuprofen) as taught by the Friedel and/or Eversmeyer reference references, to achieve the predictable result of formulating an analgesic oral dosage form for pain treatment. In addition, making and using compounds such as nabumetone and/or pharmaceutical acceptable salt thereof (as part of a combination drug) is routine and known in the art as taught by the cited references.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all cited references have demonstrate the success of making various pharmaceutical formulations comprising various analgesic compounds including oxycodone and nabumetone as well as various pharmaceutical acceptable excipients.

Discussion and Answer to Argument

9. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue "because without ibuprofen the purpose of the Baker patent... would be frustrated" and the combination of the cited references would render the "prior art invention being modified unsatisfactory for its intended purpose". (Reply, pp.7+).

Contrary to applicant's assertion, the combination of the reference would not destroy the purpose of the Baker reference for making and using pharmaceutical compositions constituting a combination of a narcotic analgesics (such as oxycodone) and a NSAID (such as ibuprofen). The purpose of the reference is in general to make and use pharmaceutical compositions with various combinations of narcotic analgesics and NSAID so that synergistic and/or additive effects of the combinations of the drugs can be utilized. For example, the Baker reference states "This patent discloses that the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone..." (Baker, col.1, lines 22+). The Baker's teaching of using a particular combination of Oxycodone and Ibuprofen is only one embodiment of the reference's teaching, and it is not the sole purpose of the reference's teaching. By

substituting one NSAID compound such as Ibuprofen with another NSAID drug such as Nabumetone to produce a pharmaceutical composition that has "greater" analgesic effects than for either alone (as stated by Baker) does not defeat the general purpose of making and using a pharmaceutical composition comprising two selected active ingredients (to achieve synergist/additive effects).

Applicant's interpretation of the Baker patent reference fails to consider the Baker patent teaching as a whole to one of ordinary skill in the art:

> "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998).

Accordingly, the Baker teaching includes Baker's entire specification and claims, inclusive of Baker's summary of the state of the prior art as illustrated in the "The Background of the Invention" (col. 1-2). In this respect, Baker '936 (col. 1-2) cites numerous prior art references starting with Sunshine et al. for the premise of making analgesic compositions by combining NSAID"s with narcotic analgesic (distinguished by merely additive analgesic effect) as well as other NSAID's (e.g. acetaminophen etc) with various narcotic analgesics, most notably oxycodone. Baker's invention (e.g. following the summary) is distinguished from the prior art by selecting compositions comprising ibuprofen as the NSAID in combination with narcotic analgesics (including oxycodone) in synergistically effective amounts while reducing

the amounts of the narcotic analgesic thus addressing the problem of addiction (pointed to at the end of the "Background of the Invention").

As stated in MPEP 2143.01 and provided by the case law:

"The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.)." (emphasis added)

In this case, the combination of the cited references would not require "a substantial reconstruction and redesign of the elements" in the primary reference (i.e. the Baker reference). Applicant's argument regarding the exclusion of ibuprofen is irrelevant because the combination of the cited references "substitutes" ibuprofen for nabumetone to achieve the predictable synergistic effects, as taught or evidenced by the cited references discussed supra. The principle of operation in Baker is making and using a pharmaceutical composition having one narcotic analgesic (such as Oxycodone) and one NSAID compound (such as ibuprofen or nabumetone) to achieve a synergistic effect. The Friedel and Eversmeyer references provide further reasoning or motivation (e.g. the advantages of using Nabumetone) to make the modification or substitution of the Baker pharmaceutical composition as discussed above. Thus, the combination of the cited references does not change the principle of operation in Baker.

Applicants also argue "the only NSAID utilized in the invention of the Baker patent... is ibuprofen" and thus "when the Baker patent is considered as a whole, is ibuprofen".. (Reply, p.11).

Similar to the discussion above, Applicant's interpretation of the "principle of operation" of the Baker reference teaching is too narrow. The "principle of operation" of the Baker reference is to combine NSAID's (e.g. ibuprofen) with opioids (e.g. oxycodone) in order to achieve improved pain relief as compared to the separate administration of the active agents. The unexpected benefit of achieving greater than additive pain relief (e.g. synergism) represents a strong teaching toward formulating additional compositions which include different (functionally equivalent) NSAID's, especially those with fewer side-effects as compared to traditional NSAID's as pointed out in the secondary reference (Eversmeyer et al; e.g. Abstract of the reference).

In addition,

> Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). See also MPEP 2121.04.

As discussed above, Baker et al teaches combinations of narcotic analgesics and NSAIDs (see col. 1-2), and do not exclude other NSAIDs from forming the combination of narcotic analgesic and NSAID that would have enhanced analgesic effect. In other words, the Baker reference does not teach that a combination of a narcotic analgesic and any of the other NSAIDs (besides ibuprofen) cannot be made or cannot be used to treat pain.

Rather, the Baker reference opens the door for developing combinations of NSAIDs and narcotic analgesics beside the combinations of ibuprofen and oxycodone. As discussed above, Baker teaches, in general, a combination of a selected NSAID and a narcotic analgesic would have enhanced analgesic effect (col. 1, lines 22+). Baker et al also demonstrated a particular

combination of the two classes of drug has enhanced analgesic effect. A person of ordinary skill in the art would be motivated to select different NSAID and/or a different narcotic analgesic to form a desired combination with enhanced analgesic effect.

Applicants also argue the cited combination of references does not teach the element of "an oral dosage form consisting of..." the two active ingredients (i.e. nabumetone and oxycodone) and at least one pharmaceutically acceptable excipient. (emphasis in original; Reply, p.8, para 5).

Applicants are respectfully directed to the body of the rejection supra for detailed discussion of the references' teaching. Briefly, the Baker reference, for example, teaches making and using pharmaceutical compositions (Tablets) consisting of oxycodone, ibuprofen, and pharmaceutically acceptable excipients (see col.4+ of Baker for list of ingredients in different tablets). As discussed supra, one of ordinary skill in the art would have been motivated to substitute nabumetone (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Friedel and/or Eversmeyer reference teachings that nabumetone is equally efficacious, but is safer with less side effects (e.g. as compared to ibuprofen). Thus, the combination of the cited references teaches all elements of the instant claims.

Applicants also assert "the Examiner has not articulated what would have suggested to one skilled in the art" to combine the cited references and/or to provide "factual" support for the prima facie conclusion of obviousness. (Reply, pp.9+).

Contrary to applicant's assertion, the previous office actions (especially, Office action, mailed 10/6/05; pp. 3+; and Office action mailed 8/1/06; pp. 10+) as well as the discussion supra have provided motivation statements and/or reasoning to combine the cited references. Contrary to applicant's assertion, "factual" supports are provided for the prima facie case of obviousness. Applicants are respectfully directed to the detailed discussion above on the specific teachings (or factual supports) of the cited references.

Furthermore, applicants are also respectfully directed to the recent Supreme Court decision, which forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396.* ("Helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents.")

Applicants also seem to argue the Examiner has not provided a specific "motivation" or reasoning to choose nabumetone instead of other known drugs (Reply, p.9). However, the other known drugs are not recited in the instant claims. Further, applicants have not provided any evidence to show the prior art would teach away from using nabumetone. As discussed supra and previously, a prima facie case of obviousness for the instant claim has been presented over the combination of the cited references.

"When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is

likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." (emphasis added; *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396).*

Applicants also seem to argue the Examiner has not demonstrated that "the results of the combination were predictable." (Reply, p.10).

Applicants are reminded that "Obviousness does not require absolute predictability" and only a "reasonable expectation of success is required". See MPEP 2143.02:

"The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (Claims directed to a method of treating depression with amitriptyline (or nontoxic salts thereof) were rejected as prima facie obvious over prior art disclosures that amitriptyline is a compound known to possess psychotropic properties and that imipramine is a structurally similar psychotropic compound known to possess antidepressive properties, in view of prior art suggesting the aforementioned compounds would be expected to have similar activity because the structural difference between the compounds involves a known bioisosteric replacement and because a research paper comparing the pharmacological properties of these two compounds suggested clinical testing of amitriptyline as an antidepressant. The court sustained the rejection, finding that the teachings of the prior art provide a sufficient basis for a reasonable expectation of success.);"

"Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness."

In this case, the prior art references teach the advantages of using Nabumetone as a member of the well know drug family NSAID (see discussion supra). The Baker reference specifically teaches the general idea of combining a narcotic analgesic compound and a NSAID compound for treatment of pain. The prior art references have all demonstrated that making and using various pharmaceutical compositions (of combinations of compounds) are routine and known in the art. Due to the advantages of the Nabumetone (such as safer, less side effects, etc.)

when compared to other drugs as well as its similar "activity" and/or "properties", as taught by Freidel and Eversmeyer, "there would have been a reasonable expectation of success".

Further, applicants have not provided any factual evidence to show "there was no reasonable expectation of success".

Baker and others con't

10. Claims **38** and **47-65** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baker** et al., (US Patent 4,569,937; 2/11/1986; cited previously), **Friedel** et al (Drugs. 1993. Vol. 45 (1): 131-156; cited previously) and **Eversmeyer** et al., (American Journal of Medicine. Aug. 1993, Vol. 95: 10S-18S; cited previously) as applied to claims 38, 47, 48 and 50-52 above, and further in view of **Oshlack** et al. US Pat. No. 5,472,712 (12/95) or **Oshlack** et al. US Pat. No. 6,294,195 (9/01: effectively filed 10/93 or earlier). The previous rejection over claims 38, and 47-52 is maintained for the reasons of record advanced in the previous office actions as well as for the reasons below. The rejection over claims 53-65 is necessitated by applicant's amendment to the claims.

The substance of the above obviousness rejection (the rejection over the combination of Baker, Friedel and Eversmeyer) is hereby incorporated by reference in its entirety.

Although the Baker reference teaches oral dosage forms which include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4) utilizing "sustained release carriers", the Baker reference does not explicitly teach "a sustained release carrier which provides a sustained release of the oxycodone and/or … salt thereof" and "a

sustained release of the nabumetone…" as recited in the instant claims 49, 59, 64, 65 etc. The Baker reference also does not explicitly teach using "an immediate release form" for nabumetone in the formulation (as recited in the instant claim 53) as well as formulation comprising particles of 0.5 to 2.5 mm in diameters as recited in the instant claims 57 and 58.

However, the use of sustained release dosage forms for opioid analgesics, including oxycodone such as utilizing sustained release carriers, beads (or particles with various diameters) as well as using immediate release formulation for non-opioid drugs in a combination drug formulation are known and routine in the art. Using beads/particles coated with the opioid drug including substrate layers which comprise the drugs is also known in the art to produce delayed release of extended duration. For examples, **Oslack** et al ('712 patent) teach drug formulation of sustained (or controlled) release formulation of various compounds including the controlled release of oxycodone (e.g. col.14, lines 15+); Oslack et al ('195 patent) also teach sustained oral formulation for opioid analgesics (e.g. Abstract) including oxycodone (e.g. col.6, lines 30+). The Oslack ('195) patent specifically teach using particles with diameters of about 0.1mm to about 3 mm (e.g. Abstract), which reads on the particles of **clms 57** and **58**. The Oslack ('195) patent also teaches using "immediate release" formulation for "a second (non-opioid) drug", incorporated into immediate release layer, or coating, etc. (e.g. col.7, lines 21+), which reads on the immediate release formulation of **clm 53** and the coating layer of **clm 59**. The Oslack ('195) reference also teaches incorporating sustained release matrix with the opioid drug (e.g. col.11, lines 30+), which reads on the sustained carrier of **clm 60**. The Oslack ('195) reference also teaches various sustained release carrier such as "hydroxyalkylcellulose" (e.g. col.11, lines 34+), which reads on the sustained carrier of **clm 55**. The Oslack ('195) reference also teaches the

sustained release formulations provide about at least 12 hour or about 24 hours, or longer release time for opioid drugs (e.g. col.5, lines 40+), which reads on the release time of **clms 54** and **61**. The Oslack ('195) reference also teaches treating pain for cancer patients (e.g. col.1, lines 50+), which the cancer pain reads on the types of pains listed in **clm 56**. Both of the references also teach the advantages of sustained release formulation. For example, the '195 patent teaches the controlled or sustained release oral dosage formulation would provide effective blood levels of the opioid analgesic for at least about 24 hours (e.g. Abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize various known and routine formulations to make various analgesic compositions that have various release rates. For examples, the sustained release carriers for oxycodone including beads/layers as well as the immediate release formulations for the other non-opioid drug in the same formulation as taught by the Oshlack and Oshlack et al. patents. A person of ordinary skill in the art would have been motivated at the time of the invention to use the various formulations as disclosed in Oshlack references (i.e. the various time releasing formulations) to make a combination drug based on a sustained releasing opioid drug (such as oxycodone) and an immediate releasing non-opioid drug (such as nabumetone), because Baker et al and Oshlack ('195) patent specifically teach "sustained release formulations" for the opioid drug is known and routine, and the advantages of utilizing the Oshlack patent sustained release carriers including delayed drug release of extended duration especially for treatment of cancer pains. In addition, it would have been obvious to one of ordinary skill in the art to apply the standard technique of formulating sustained release formulation (especially for oral administering an opioid analgesic such as oxycodone) as taught by both the Oshlack patent

references, to improve the delivery of the analgesic compounds for the predicable result of enabling standard pharmaceutical formulation and administering.

A person of ordinary skill in the art would have been motivated at the time of the invention to use immediate or sustained release formulation for the non-opioid drug (such as Nabumetone) in the same combination drug formulation, because Oshlack ('195) patent teaches the advantages of using immediate release formulation such as an "immediate releasing layer" to coat the opioid drug to afford differential drug release rates for efficient pain treatments. In addition, because all the cited references teach methods of making various combinations of drugs in the same pharmaceutical composition with various releasing matrices, coating, particles, etc., for various pain treatments, it would have been obvious to one skilled in the art to substitute one type of releasing formulation (such as sustained release) for the other (such as immediate release or combinations of sustained and immediate release formulations) to achieve the predictable result of making pharmaceutical composition with optimized drug releasing rates.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of making and using various drug formulations (including sustained/immediate release formulations, coating, tablets, particle matrix, etc.) especially for various analgesic compounds.

Discussion and Answer to Argument (103 art rejection)

11. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed the above rejection with the same argument as the traversal over the combinations of "Baker, Friedel and Eversmeyer" references. Thus, applicants are respectfully directed to the discussion under "Baker, Friedel and Eversmeyer" for answer to arguments.

New Claim Objection(s) / Rejection(s)

Claim Objections

12. Claim **57** and **58** are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claim 57 recites "said dosage form comprises…" which transition phrase is open-ended (i.e. expanding the scope of the "dosage form") and does not further limit the close-ended transition phrase "consisting of" as recited in the instant claim 53. (see MPEP 2111.03) The instant claim 58 depends on the instant claim 57, and ultimately depends on the instant claim 53, and thus also does not further limit the instant claim 53. This claim objection is necessitated by applicant's amendments to the claims.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by applicant's amendments to the claims.

Claim 56 recites "said pain is cancer pain, post-surgical pain... and common cold" (emphasis added), which is unclear and indefinite. It is not clear if the instant claim language is intended to recite the "said pain" comprise all the different types of pain listed in the instant claim or if the instant claim is reciting a Markush group. Applicants are respectfully directed to MPEP 2173.05(h) for proper alternative expression such as a Markush group:

> Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See Ex parte Markush, 1925 C.D. 126 (Comm'r Pat. 1925).
>
> When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, if "wherein R is a material selected from the group consisting of A, B, C and D" is a proper limitation, then "wherein R is A, B, C or D" shall also be considered proper.

The instant claim 56 also seems to recite "said pain" is, for examples, "viral infections" and/or "common cold", which the said viral infections and/or common cold are diseases but not types of pain.

Applicants are requested to clarify the instant claim language to recite proper alternative format.

Claim Rejections - 35 USC § 103

15. The text of those sections of Title 35, U.S. Code is recited supra in the instant Office action.

Mayer and Others

16. Claims **38, 47-52** and **62-65** are rejected under **35 U.S.C. 103(a)** as being unpatentable over Mayer et al (US 5,840,731; 11/24/1998; filed on 8/2/1995; cited previously), and if necessary in view of **Friedel** et al (Drugs. 1993. Vol. 45 (1): 131-156; cited previously) and **Eversmeyer** et al., (American Journal of Medicine. Aug. 1993, Vol. 95: 10S-18S; cited previously). This rejection is necessitated by applicant's amendments to the claims.

Mayer et al, throughout the patent, teach methods of treating pain using various drug compositions (see Abstract; Claim 2), which reads on the claimed treatment method of **clms 38** and **62**.

The reference also teaches the compositions of drugs can be combinations of drugs (e.g. col.1, lines 24+), and especially combination between Opioid analgesics and NSAIDS (e.g. col.1, lines 50+). The reference also teaches "the first component of the drug composition" is an opioid such as "oxycodone" and/or their pharmaceutically acceptable salts (e.g. col.3, lines 57+). The reference also teaches "the second component of the drug composition" is "of the nonopioid type… of any of the foregoing" (col.4, lines 11+), and the reference discloses the nonopioid analgesics includes "nabumetone" and/or its pharmaceutically acceptable salts (col.3-4; bridging). These passages of the reference teach a composition for pain treatment comprising oxycodone and nabumetone of **clms 38** and **62.**

The reference also teaches pharmaceutical acceptable carriers (e.g. col. 5), which reads on the component of **clms 38**, **48** and **62**. The reference also teaches, for example, 4.5 mg of oxycodone (see Table in between cols. 5-6), which reads on the dosage amount of **clm 52**.

The reference also teaches various amounts of the "first" and "second" components of the drug (e.g. col.5-6; Examples), which read on the ratios recited in **clms 47** and **63**.

The reference also teaches using various drug formulations such as gelatin capsules (e.g. col.5, lines 5+), which reads on the sustained release carriers of **clms 49**, **50**, **64** and **65**.

The Mayer reference does not explicitly teach using "an oral dosage form consisting of (i) nabumetone… (ii) oxycodone… and (iii) at least one pharmaceutically acceptable excipient" as recited in **clms 38** and **62**.

However, the Mayer reference teaches a number of drug combinations for alleviating pain… are known" (e.g. col.1, lines 24+). As discussed supra, the Mayer reference also teaches combination of an opioid drug such as oxycodone and a NSAID drug such as nabumetone is known in the prior art to be effective analgesic (e.g. cols.3-4). In addition, the Mayer reference also teaches the necessary ingredient of pharmaceutically acceptable excipient as part of a pharmaceutical composition (e.g. col.5).

In addition, **Friedel** et al. teach that nabumetone (and/or pharmaceutical acceptable salt thereof) possesses the typical pharmacodynamic properties of the nonsteroidal class of anti-inflammatory (NSAID) drugs including intrinsic analgesic and antipyretic activity being demonstrated in animal studies and in humans with the following advantages over other NSAIDS:

a. does not exert a significant direct toxic effect on the gastric mucosa during absorption;

b. in studies, produced a lower incidence of gastrointestinal erosions or microbleeding than aspirin, naproxen, piroxicam and ibuprofen; and

c. more recently clinical data further confirmed the efficacy and tolerability of nabumetone ; "Thus, the drug (e.g. nabumetone and/or pharmaceutical acceptable salt thereof) should now be considered a well established member of this group of agents (e.g. NSAIDS) for the treatment of painful rheumatic and inflammatory conditions". See e.g. Abstract, pages 132-133 as well as the remainder of Friedel.

In addition, the Friedel reference also teaches various dosage amounts (such as 1000 mg-1500 mg) of nabumetone can be used for various treatment depending on the severity of the symptoms (e.g. p.133, bottom), which reads on the amount of nabumetone as recited in **claim 51**.

Similarly, **Eversmeyer** et al. teach that nabumetone is equally efficacious in the treatment of arthritic pain patients (e.g. osteo/rheumatoid arthritis) but has shown to be more safe, with reduced side-effects (e.g. dyspepsia, ulcers, reduced hemoglobin, gastritis etc.). See Eversmeyer et al. Abstract and disclosed studies.

Accordingly, one of ordinary skill in the art would have been motivated to combine nabumetone (a NSAID) and/or pharmaceutical acceptable salt thereof with Oxycodone (an opioid analgesic) in light of the Mayer, the Friedel and/or Eversmeyer reference teachings that nabumetone is equally efficacious, but is safer with less side effects.

Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose.

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to make and use an oral dosage form consisting of only oxycodone and nabumetone with at least one pharmaceutically acceptable excipient.

A person of ordinary skill in the art would have been motivated at the time of the invention to make and use an oral dosage form consisting of only oxycodone and nabumetone (with an appropriate amount) with at least one pharmaceutically acceptable excipient, because dosage forms of combinations of analgesic drugs (such as oxycodone and nabumetone) are routine and known in the art. In addition, the Mayer reference teaches the advantages of making and using pharmaceutical composition comprising a combination of an opioid drug and a NSAID drug so that a synergistic effect can be achieved. Further, the Friedel and/or Eversmeyer references teach the advantages of Nabumetone. Because the Mayer reference teach methods of making and using various drug formulation comprising different combinations of an opioid drug and a NSAID drug, it would have been obvious to one skilled in the art to substitute one drug for the other to achieve the predictable result of making and using routine analgesic pharmaceutical composition. It would have been obvious to one of ordinary skill in the art to apply the standard technique of adding at least one "pharmaceutically acceptable excipients" as taught by Mayer et al, to improve pharmaceutical formulation for the predicable result of enabling standard making and using a pharmaceutical composition for treatment of pain.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Mayer et al have demonstrated the success of generating and using various pharmaceutical formulations.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Patent Examiner, Art Unit 1639
10/8/08